Dihydrotanshinone: A Pan-Therapeutic Treatment for Chemoresistance in Cancer

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Glioblastoma is the most common and aggressive type of brain tumor in adults, primarily treated with the chemotherapeutic agent Temozolomide (TMZ). However, many tumors are initially resistant to or develop resistance to TMZ, mainly due to high levels of O6-methylguanine DNA transferase (MGMT), which repairs the DNA damage caused by TMZ. Research reported here focused on reversing TMZ resistance by combinatorial treatment with Dihydrotanshinone (DHT), an analogue of which is currently in clinical trials for childhood leukemia (APL). DHT in combination with TMZ displayed a synergistic, selectively cytotoxic, oncolytic effect in a MGMT-deficient cell line and a sensitizing effect to TMZ in a MGMT-expressing cell line, as confirmed by the Combination Index Synergy Algorithm. Cytotoxicity due to DHT was shown to be reactive oxygen species dependent, as suggested by a computational molecular docking model. Importantly, DHT was shown to penetrate the blood-brain barrier in a novel in vitro co-culture model, verified by the TEER method and various permeability dyes. The interaction between DHT and TMZ was found to be a result of the synergistic reduction of protein and mRNA expression of MGMT and P-glycoprotein, a critical drug transport channel. Differential gene expression was assessed via DNA microarray and protein expression via enzyme linked immunosorbent assay. Additionally, the NfkB complex and AKT activity were sensitive to combinatorial treatment, revealing the mechanism of action of the combinatorial strategy. DHT was shown to augment TMZ efficacy, indicating that, since DHT can penetrate the blood–brain barrier, TMZ in combination with DHT may represent a promising therapeutic option for glioblastoma.

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